N-Methylimidazole-Promoted Efficient Synthesis of Functionalized 1,3-Oxazoline-2-thiones under Solvent-Free Conditions

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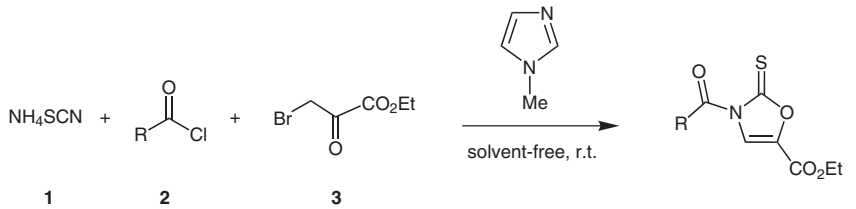
Received 12 February 2008

Abstract: An efficient synthesis of ethyl 2-thioxo-2,3-dihydro-1,3-oxazole-5-carboxylates or ethyl 5-methyl-2-thioxo-2,3-dihydro-1,3-oxazole-4-carboxylates, under solvent-free conditions, is described via reaction between ammonium thiocyanate, acid chlorides, and ethyl bromopyruvate or ethyl 2-chloroacetoacetate in the presence of *N*-methylimidazole.

Key words: oxazole, ethyl bromopyruvate, *N*-methylimidazole, ammonium thiocyanate, benzoyl chloride, ethyl 2-chloroacetoacetate

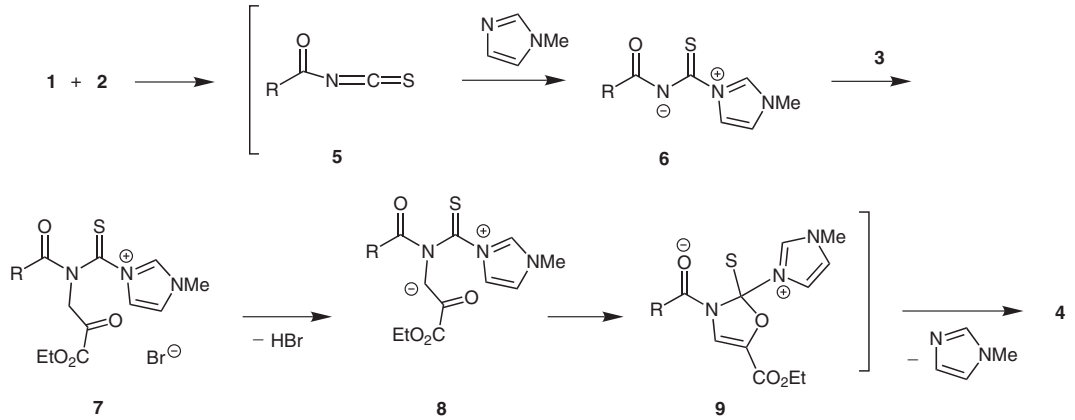
1,3-Oxazoline-2-thiones possess a simple heterocyclic frame which has been barely explored compared to its nonaromatic counterpart 1,3-oxazolidine-2-thione, with only relatively simple precursors related to α-hydroxyketones having been converted into 1,3-oxazoline-2-thiones.[1,2] Syntheses of 1,3-oxazoline-2-thiones have been reported using condensation of either thiocyanic acid[3–6] or isothiocyanates[7] with an α-hydroxycarbonyl substrate, or condensation of thiophosgene with an aminoketone.[8] The balance of reactivity of α-hydroxycarbonyl systems with thiocyanic acid toward the formation of either 1,3-oxazolidine-2-thione or 1,3-oxazoline-2-thione has been reported recently.[9,10]

As part of our current studies on the development of new routes in heterocyclic synthesis,[11–13] we report an efficient synthetic route to functionalized 1,3-oxazoline-2-thiones. Thus, the reaction of ammonium thiocyanate (**1**), acid chlorides **2**, ethyl bromopyruvate (**3**) in the presence of *N*-methylimidazole (20 mol%), under solvent-free conditions, produced ethyl 2-thioxo-2,3-dihydro-1,3-oxazole-5-carboxylates **4** in good yields[14] (Scheme 1).



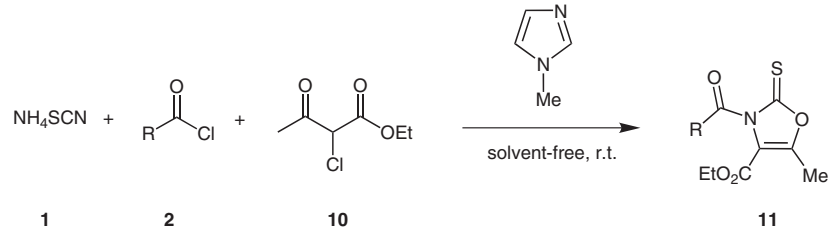
2, 4	R	Yield (%) of 4
a	Ph	85
b	4-MeC_6H_4	95
c	4-BrC_6H_4	75
d	4-ClC_6H_4	70
e	4-$O_2NC_6H_4$	85
f	*t*-Bu	83
g	Et	86

Scheme 1



Scheme 2

SYNLETT 2008, No. 9, pp 1287–1288
Advanced online publication: 07.05.2008
DOI: 10.1055/s-2008-1078403; Art ID: D05208ST



2, 11	R	Yield (%) of 11
a	Ph	85
b	4-MeC_6H_4	80
c	4-BrC_6H_4	76
d	4-$O_2NC_6H_4$	75

Scheme 3

The structures of compounds **4a–g** were assigned by a consideration of their IR, ^{1}H NMR, ^{13}C NMR spectroscopic and mass spectrometric data. The ^{1}H NMR spectra of **4a–g** exhibited characteristic signals for methine (δ = 7.52–7.64 ppm) protons. The ^{13}C NMR spectra of the 1,3-oxazoline-2-thione ring system of **4a** showed signals at δ = 118.4 (CH), 139.8 (C), 156.6 (C=O), 176.7 (C=O), and 178.1 (C=S) ppm. The mass spectra of **4a–g** displayed the molecular ion peaks at appropriate *m/z* values.

A tentative mechanism for this transformation is proposed in Scheme 2. The reaction starts with the formation of isothiocyanate **5**, followed by addition of *N*-methylimidazole and formation of the 1:1 adduct **6**, which is subsequently attacked by ethyl bromopyruvate to produce **7**. Intermediate **7** subsequently undergoes cyclization and loss of *N*-methylimidazole to generate **4**.

To extend our knowledge of this reaction, we performed the reaction between ethyl 2-chloroacetoacetate (**10**), ammonium thiocyanate, and acid chlorides **2** in the presence of *N*-methylimidazole (20 mol%). This reaction led to the formation of ethyl 3-aroyl-5-methyl-2-thioxo-2,3-dihydro-1,3-oxazole-4-carboxylates **11** in good yields[14] (Scheme 3).

Compounds **11a–d** were again fully characterized according to their elemental analyses and IR, ^{1}H NMR and ^{13}C NMR spectra.

In conclusion, the reaction between ethyl bromopyruvate or ethyl 2-chloroacetoacetate, ammonium thiocyanate, and acid chlorides in the presence of *N*-methylimidazole (20 mol%) leads to the functionalized 2-thioxo-2,3-dihydro-1,3-oxazoles in good yields. This procedure has the advantage that the reaction is performed under neutral conditions, and the starting materials can be used without any preactivation or modification.

References and Notes

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(14) **General Procedure for the Preparation of Compounds 4 and 11**: A stirred mixture of ammonium isothiocyanate (0.15 g, 2 mmol) and acid chloride **2** (2 mmol) was warmed at about 90 °C in a water bath for 5 min and ethyl bromopyruvate (0.39 g, 2 mmol) or ethyl 2-chloroaceto acetate (0.33 g, 2 mmol) was added slowly. The mixture was allowed to cool to r.t. and *N*-methylimidazole (0.032 g, 20 mol%) was added. The reaction mixture was stirred for 12 h and extracted with Et_2O (2 mL) to afford the pure title compounds.
Compound **4a**: pale yellow crystals; yield: 0.38 g (85%); mp 129–131 °C. IR (KBr): 1724, 1631, 1585, 1518, 1470 cm^{-1}. ^{1}H NMR: δ = 1.45 (t, ^3J = 7.2 Hz, 3 H, Me), 4.46 (q, ^3J = 7.2 Hz, 2 H, OCH_2), 7.52 (t, ^3J = 7.8 Hz, 2 H, 2 × CH), 7.61 (*t*, ^3J = 6.1 Hz, 1 H, CH), 7.65 (s, 1 H, CH), 7.52 (d, ^3J = 6.1 Hz, 2 H, 2 × CH). ^{13}C NMR: δ = 14.6 (Me), 63.0 (OCH_2), 118.4 (CH), 128.9 (2 × CH), 130.5 (2 × CH), 133.8 (CH), 134.9 (C), 139.8 (C), 156.6 (C=O), 176.7 (C=O), 178.1 (C=S). EI–MS: *m/z* = 227 (10) [M$^+$], 121 (20), 105 (100), 77 (90), 57 (30), 51 (64), 45 (36). Anal. Calcd for $C_{13}H_{11}NO_4S$ (277.29): C, 56.31; H, 4.00; N, 5.05. Found: C, 56.30; H, 4.03; N, 5.00.
Compound **11a**: white powder; yield: 0.49 g (85%); mp 140–142 °C. IR (KBr): 1720, 1635, 1582, 1510, 1475 cm^{-1}. ^{1}H NMR: δ = 1.38 (t, ^3J = 7.2 Hz, 3 H, Me), 2.68 (s, 3 H, Me), 4.34 (q, ^3J = 7.2 Hz, 2 H, OCH_2), 7.48 (t, ^3J = 7.5 Hz, 2 H, 2 × CH), 7.58 (t, ^3J = 7.5 Hz, 1 H, CH), 8.31 (d, ^3J = 7.5 Hz, 2 H, 2 × CH). ^{13}C NMR: δ = 13.8 (Me), 14.1 (Me), 62.0 (OCH_2), 110.4 (C), 128.4 (2 × CH), 129.9 (2 × CH), 133.1 (CH), 134.8 (C), 155.5 (C), 160.6 (C=O), 176.1 (C=O), 177.5 (C=S). EI–MS: *m/z* = 291 (15) [M$^+$], 186 (78), 105 (100), 77 (48), 45 (48). Anal. Calcd for $C_{14}H_{13}NO_4S$ (291.32): C, 57.72; H, 4.50; N, 4.81. Found: C, 57.76; H, 4.54; N, 4.80.